Abstract and Introduction

Abstract

Huntington's disease is a devastating illness, although its autosomal-dominant genetic transmission allows a unique opportunity to study apparently healthy individuals before manifest disease. Attempts to study early disease are not unique in neurology (e.g., mild cognitive impairment and vascular cognitive impairment), but studying otherwise healthy-appearing individuals who have nearly 99% certainty of manifesting the symptoms of brain disease does provide distinct but valuable information about the true natural history of the disease. The field has witnessed an explosion of research examining possible early indicators of Huntington's disease during what is now referred to as the 'prodrome' of Huntington's disease. A NIH study in its 9th year (PREDICT-HD) has offered a glimpse into the transition from an apparently healthy state to an obviously diseased state, and can serve as a model for many other genetic diseases, both neurological and non-neurological.

Introduction

Publication of the human genome has accentuated the desired paradigm shift in medicine from treatment of disease following diagnosis to the prediction and prevention of disease in healthy individuals. Huntington's disease (HD), an autosomal-dominant progressive neurological disease with an identified gene mutation,[1] has proven helpful to expedite preparations for preventive clinical trials in neurodegenerative diseases. This is because individuals with the gene mutation can be identified years before clinical diagnosis through genetic testing. HD is a neurodegenerative disorder with loss of medium GABAergic spiny neurons, sparing of the large cholinergic interneurons,[2,3] and specific neuronal loss in layers V and VI of the cerebral cortex.[4] These physiological changes lead to an insidious decline in motor, cognitive and psychiatric functioning, a diminished quality of life and premature death for individuals carrying the expanded polyglutamine repeat sequence.[5] Age at disease diagnosis is associated with length of the expanded gene mutation, such that individuals with longer repeat lengths have a younger age at diagnosis.[6,7]

This review examines the earliest signs and symptoms observed in individuals carrying the gene expansion for HD who do not meet criteria for clinical diagnosis of disease. These groups of so-called 'at-risk' participants have been referred to as 'asymptomatic', 'presymptomatic', 'preclinical', 'prediagnosed', 'premanifest', 'pre-HD' or 'prodromal HD'. Regardless of the label, research participants with a known expansion in the HD gene but no clinical diagnoses provide an incomparable opportunity to identify the earliest neurobiological and clinical changes in brain disease. We use the term 'prodrome' to describe the phase precursory to the manifestation of full disease; the shorthand 'pre-HD' will be used throughout this review to represent the HD prodrome.

Several clinical trials are investigating means to alleviate or reduce symptoms and slow progression in clinically diagnosed HD.[8,201] Consistent with other medical conditions, treatments might be ideally initiated at or before the earliest signs of disease. There are at least two primary challenges to the design of clinical trials for pre-HD: selection of participants who are most likely to show measurable change over the course of a clinical trial, and development of outcome measures that are sensitive to interventions and can demonstrate variation over the natural history of pre-HD. In order to meet these and other challenges to preventive clinical trials, indicators of very early disease are required. Attempts to detect HD earlier by studying individuals in the HD prodrome will be reviewed.

PREDICT-HD Study

Neurobiological Predictors of Huntington's Disease (PREDICT-HD; NS40068, Principal Investigator Jane S Paulsen) is a multinational, longitudinal, observational study aimed at identifying biological and refined clinical markers of pre-HD in humans, and then validating the optimal marker(s) and clinical end points for use in preventive clinical trials. Participants recruited from 32 sites across the USA, Canada, UK, Germany, Spain and Australia undergo annual study visits consisting of a neurological motor examination, cognitive assessment, brain magnetic resonance imaging (MRI), psychiatric and functional rating scales and blood tests for genetic and biochemical analyses.[9,10]

Currently in its 9th year of funding by the NIH and Cure HD Initiative (CHDI) Foundation (CT, USA),[202] PREDICT-HD has enrolled...
more than 880 gene-expanded, but not clinically diagnosed, participants, as well as a smaller sample of demographically matched, nongene-expanded participants (n = 220) that serve as a comparison group. To date, 127 participants from the PREDICT-HD study have been prospectively clinically diagnosed. Clinical diagnosis refers to the current standard for the diagnosis of HD; when a movement disorder specialist is 99% sure that 'unequivocal extrapyramidal signs' are present or in a person with a family history of HD. In addition, a proxy measure of 'estimated years to HD clinical diagnosis' was developed and validated using gene mutation and current age. Studies using pre-HD participants often use measures to estimate or 'predict' eventual diagnosis using formulae similar to the one cited above. When such formulas are used they are described as 'estimated' diagnosis, which is distinct from actual clinical diagnosis. This article summarizes published literature in pre-HD, as well as findings from PREDICT-HD. The HD field has witnessed exciting research growth; the number of HD publications has increased fourfold over the past 9 years. This review provides a summary intended to facilitate greater interest in this promising area of research, encourage other research groups to consider earlier detection of disease in healthy individuals and document challenges to future progress.

**Neuroimaging Indicators of pre-HD**

Structural neuroimaging measures in HD historically emphasized the basal ganglia and have been demonstrated to be related to disease duration, magnitude of dementia, severity of movement disorder, cognitive performance, functional capacity and longer CAG repeat lengths. However, more recently, two major paradigm changes in HD research have occurred. First, since it is established that over 50% of cell death has already occurred at the time of clinical diagnosis and that cognitive, sensory and psychiatric abnormalities often precede motor symptoms in HD, neuroimaging in pre-HD has become of primary interest. Second, with ongoing and rapid advances in technology, coupled with longstanding indications of extrastriatal involvement in HD, more recent efforts in HD neuroimaging have involved whole-brain investigation. Findings have included cerebral spinal fluid volumes, regional cortical degeneration, abnormal thinning of cortical sulci, whole-brain atrophy and significant grey and white matter loss, even in very early and pre-HD. White matter findings have been further explored in HD with the application of diffusion tensor imaging, demonstrating that fractional anisotropy is both increased and decreased significantly, and depends upon the specific stage of early HD (Figure 1). Importantly, diffusion tensor imaging has indicated that tissue changes were apparent in pre-HD participants in the absence of significant white matter volume loss, suggesting that subtle morphological alterations occur before the overt death of neurons.

**Figure 1. Diffusion tensor functional anisotropy group statistical maps. (A) Pre-Huntington's disease. (B) Huntington's**
disease. Exploratory whole-brain analyses demonstrated significant reductions in functional anisotropy in the internal capsule, frontal subcortical WM and portions of the thalamus, and increases in functional anisotropy in the putamen in the group of presymptomatic individuals known to carry the genetic mutation that causes Huntington's disease (pre-Huntington's disease), paralleling the results of the region of interest analysis. In the early-stage Huntington's disease group, significant increases in the putamen and globus pallidus were observed; reductions in functional anisotropy included the internal capsule, corpus callosum, external/external capsule, cerebral peduncles, brainstem and WM underlying brain regions, including sensorimotor cortex, frontal, parietal and parieto-occipital areas. Blue areas show areas of statistically significant increases in functional anisotropy; yellow areas show areas of statistically significant reductions in functional anisotropy.

WM: White matter.
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However, despite efforts to consider all brain changes associated with early HD, the few reports that have conducted comparisons among imaging indices report the prominence of the basal ganglia. For instance, an examination of percentage volume loss for each brain region demonstrated that striatal volume loss was as great as, or greater than, any other structure examined. An effect size analysis of each brain region validated the percentage volume loss and suggested that the most robust differences between matched normal comparison participants were in the basal ganglia regions (Figure 2).[35-37]

![Figure 2. Volume differences and effect sizes based on comparisons of demographically matched normals and pre-Huntington's disease less than 10 years from estimated motor diagnosis.](image)

GM: Grey matter; WM: White matter.

However, efforts to determine whether brain changes are somewhat independent of one another have revealed that regional cortical thinning, as well as white matter atrophy, both provide independent contributions to aspects of disease beyond contributions made by the striatum alone. For instance, cortical surface reconstruction maps show that regional cortical thinning in pre-HD remains when adjusting for caudate and putamen volumes (Figure 3).[25] Similarly, a multiple regression analysis on estimated motor diagnosis suggested that white matter volume loss made a significant contribution to the predicted number of years to clinical diagnosis that was above and beyond contributions made by the striatal volumes alone.[35-37]
Figure 3. Evidence of regional cortical thinning in pre-Huntington’s disease and its relationship to striatal volume. 
**Cortical surface reconstruction maps.** Significant cortical thinning was present in the pre-Huntington’s disease group compared with controls. When adjusting for caudate volumes, the intergroup variance in thinning was less prominent over portions of superior temporal gyrus; when adjusting for putamen volumes, variance was less prominent over posterior frontal regions. Some areas of thinning appeared to be independent of caudate or putamen volumes. Maps are displayed on an average composite brain, with areas of more thinning transitioning from red (p < 0.05) to yellow (p < 0.001), unadjusted for multiple comparisons.

L: Left; R: Right.
Reproduced with permission from [25].

Since structural imaging measures appear to be biomarker candidates for pre-HD clinical trials, consideration of marker purpose is essential. Rapid screening tools for clinical trial inclusion will demand imaging measures that are feasible in terms of time, cost and burden. Recently, some research groups have made efforts to produce and validate imaging protocols that meet these criteria. Progress has included voxel-based morphometry,[38] multivariate support vector machines[39] and automated artificial neuronal network segmentations.[10,23,27,35-37] Although few of these measures have undergone longitudinal study, there is some evidence of adequate and reliable change indices.[40,41] For example, Aylward and colleagues presented MRI data from nearly 200 pre-HD individuals and 60 controls, scanned at both baseline and 2-year follow-up.[36] Pre-HD participants were divided into groups based on proximity to estimated clinical diagnosis: far (> 15 years from estimated diagnosis); mid (9-15 years); and near (< 9 years). All pre-HD groups showed a faster rate of atrophy than controls in striatum and cerebral white matter, although annual percentage change was greater in striatum than cerebral white matter. However, when normal age-related atrophy (i.e., change observed in the control group) was taken into account, there appeared to be more disease-related atrophy in white matter than in striatum. The authors concluded that measures of volume change in both the striatum and white matter may serve as good outcome measures for future clinical trials in pre-HD. These findings emphasize the importance of normal comparison participants in the interpretation of pre-HD findings and in the design of preventive clinical trials.

In most brain disorders, there is accumulating evidence that the clinical signs of disease do not simply depend on the extent of tissue destruction, but rather represent a complex balance among neuronal dysfunction, tissue repair and circuitry reorganization. It is generally accepted that neurons endure a period of dysfunction prior to death. Structural imaging characterizes brain volume and...
cell loss, whereas functional imaging portrays brain performance and cell dysfunction. Based upon this distinction, functional neuroimaging modalities may be more sensitive to the earliest changes in HD than structural imaging approaches. Functional imaging findings in pre-HD have proven to be somewhat consistent, demonstrating alterations even when minimal or no volume loss is evident.

Several positron emission tomography (PET) measures in pre-HD are abnormal prior to motor diagnosis, including D1 and D2 dopamine receptor binding, peripheral benzodiazepine binding using $^{11}$C-(R)-PK11195 (PK) and glucose metabolism. Longitudinal PET studies have suggested annual changes in pre-HD ranging from 2.3 to 10.9% per year. Considering the relatively large longitudinal effect sizes suggested by these data, PET measures may prove cost effective as an outcome for preventive clinical trials. Further research is essential to determine whether PET might offer greater sensitivity, larger effects and consequential smaller sample sizes for clinical trial design. In addition, magnetic resonance spectroscopy (MRS) has advantages over PET in terms of availability and cost, but has reported conflicting results, suggesting that further research elucidating inconsistent findings and assurances of reliability is needed.

Functional MRI (fMRI) has been most frequently used as a tool to understand and document early changes in brain function associated with pre-HD. Although abnormalities are consistently detected, patterns and interpretations are mixed. A more complete review of functional imaging in HD has been produced elsewhere. Briefly, consistent differences in activation patterns and lateralization effects are found between HD, pre-HD and normal controls, which vary dependent on the disease stage. One pattern is characterized by hyperactivation in pre-HD further from diagnosis, followed by hypoactivation in pre-HD closer to diagnosis. Although activation circuits vary depending on the cognitive paradigm used, this general finding has been replicated across studies. Reduced activation in pre-HD has been described by more studies, despite variation in tasks. These fMRI activation patterns that emerge across studies are well depicted by Zimbleman and colleagues who report all three patterns: equivalent activations between normal comparisons and pre-HD estimated to be far from diagnosis with diminished activations in pre-HD closest to motor diagnosis; stepwise decreases in activations as diagnosis approaches; and hyperactivations in pre-HD far from diagnosis with hypoactivations in pre-HD closer to diagnosis (Figure 4).

**Figure 4. Magnetic resonance imaging signal changes.** (A) Percentage MRI signal change for each region of interest in which the far group showed significantly greater activation relative to the close and control groups (i.e., far > cont = close). (B) Percentage MRI signal change for each region of interest in which a step-wise reduction in activation was observed between the three groups (i.e. cont > far > close). (C) Percentage MRI signal change for each ROI in which the close group showed significantly lower activation relative to the far and control groups (i.e., cont = far > close).

Error bars = standard error of the mean.
CMA: Cingulate motor area; Cont: Control; L: Left; MRI: Magnetic resonance imaging; R: Right; SMA: Supplementary motor area; STG: Superior temporal gyri.
Although careful comparison and further study are needed to disentangle fMRI in pre-HD, the factors to consider are clear and will be mentioned here in order to encourage careful cross-study comparisons of future research. First, estimations of proximity to motor diagnosis have recently been validated[13] and a consistent utilization of the validated formula would improve cross-study comparisons of samples. The diagnosis estimation formula requires that CAG repeat length and current age are considered in the estimate. Second, cognitive assessment performances are essential to determine whether cognitive impairment is evident, since some studies found that pre-HD with apparently intact cognitive performances may be using compensatory strategies to achieve normal performances, and may be more likely to demonstrate hyperactivations in other brain areas with or without hypoactivations in the caudate. Third, structural analysis of volume loss is key to ascertain whether hypoactivations reflect decreased volume. Stratifying groups based on striatal volumes assists with staging of pre-HD, because groups shown to have normal striatum volumes and normal cognitive performances are less likely to show striatal hypoactivation. Finally, consistent use of clinical rating scales will allow all participants to be assessed on the same metric of clinical motor manifestation and diagnosis.[11]

This brief summary provides ample support for the utility of imaging in the detection and tracking of disease in pre-HD. Future research in this area will be most beneficial when addressing one of three questions. First, does the imaging measure being studied improve upon current available measures? The measure should be compared with regard to reliability, cost and effect size. That is, a new measure that has greater consistency, less cost and larger effect sizes for pre-HD change over time might be a better outcome measure than striatal volume. Second, does the imaging measure add nonredundant information? If a new imaging measure was not highly associated with striatal volume and represented an additional component of the disease process (as is suggested by white matter), the measure may suggest new directions for understanding mechanism, treatment development or further reducing sample size by increasing power. Third, imaging measures have not undergone adequate validity studies to determine whether they remain equally effective outcome measures at varying stages of disease.[24] For example, clinical trials designed to follow participants long past clinical diagnosis are likely to require measures in addition to striatal atrophy, which the utility of this measure diminishes with the size of the caudate in diagnosed patients. It is not yet known how late in the HD stages this imaging measure remains valid. The studies described in this summary will make significant contributions to the design of preventive clinical trials for pre-HD.

**Motor Signs**

The motor signs and symptoms of HD have received the most attention in both clinical care and early research. Many research studies have examined the utility of the neurological examination for the early measurement of HD in at-risk individuals. Two studies with sufficient sample sizes report that subtle changes in motor function are present in HD gene expansion carriers who do not exhibit sufficient motor signs to make a clinical diagnosis of HD.[59,60] More specifically, the most sensitive signs included minimal chorea of the extremities and slowing of oculomotor functions. In the largest pre-HD sample studied to date, Biglan and colleagues examined 926 participants at risk for HD (733 cases and 196 controls) and found that elevated total motor scores at baseline were associated with estimated clinical diagnosis (partial $r^2$: 0.14; $p < 0.0001$) and smaller striatal volumes (partial $r^2$: 0.15; $p < 0.0001$).[61] Nearly all motor domain scores showed greater abnormality with increasing proximity to estimated clinical diagnosis, although bradykinesia and chorea were most highly associated with diagnostic immediacy. Among individual motor items, worse scores on finger tapping, tandem gait, the three-step Luria, saccade initiation and chorea show unique association with diagnosis probability. Although longitudinal studies of motor progression in the pre-HD epoch are few, findings are mixed. Solomon and colleagues report accelerating motor declines as diagnosis approaches,[62] whereas Witjes-Ane and colleagues suggest that no measures show decline over time and that more sensitive assessment tools are needed.[63]

Although the motor exam may be the most widely used method of assessing motor signs in HD, supplementary methods, such as video motion analysis[64] and quantitative eye and motor measures,[65] have been explored. Using quantitative motor assessments (i.e., force transducer, GAITrite and saccadometer) Tabrizi et al.[28] found greater antisaccade error rates and greater tongue protrusion variability in diagnosed HD and in pre-HD with more disease burden.[28,66] Georgiou-Karistianis and colleagues used motor tasks that involve variations in cognitive load and found that difficulty inhibiting automatic responses, movement times and reaction times for cognitive tasks are associated with estimated diagnosis.[67] Golding and colleagues suggest that saccadic slowing and delayed reflexive saccades are evident only in diagnosed HD, whereas pre-HD demonstrates slowing in voluntary-guided saccades, associated with estimated diagnosis.[68] Bleker and colleagues compared a video-based eye tracking system with clinical ratings and reported that antisaccades and memory-guided eye movements were more sensitive and may provide a more objective and sensitive method to quantify early HD.[69] Antoniadis and colleagues provide a theoretical explanation for saccade measurements in pre-HD, suggesting that very early eye movements might reflect an impairment of the tonic suppression of the colliculus, normally mediated by pathways through the basal ganglia.[70] Finally, Rao and colleagues used a computerized...
walkway that recorded spatiotemporal variables and reported that pre-HD volunteers demonstrated reduced gait velocity, decreased stride length and greater variability in step time, which were associated with estimated diagnosis. Despite many efforts to utilize improved technology to better assess early motor signs of HD, findings have been mixed and future studies will require careful comparison of published and new findings in order to better understand how quantified motor abnormalities might better detect pre-HD.

Since the clinical diagnosis of HD is based upon motor abnormalities, it is no surprise that subtle motor signs are predictive of eventual clinical diagnosis. However, what is unclear is whether improved motor measures might decrease the variability observed in clinical ratings and diagnoses. Decreased variance is readily translated into increased power for clinical trials. On this basis alone, the importance of improved reliability of the motor examination and the development of improved motor measures are paramount for improved clinical trials in all movement disorders. A comprehensive review of early motor signs in pre-HD is required that details how to standardize the motor examination for pre-HD. Future research exploring quantitative methods of motor assessment (such as GAITrite and saccodometry) could then be directly compared with clinical ratings in order to determine whether the increased sensitivity attained is worth the extra cost required by the inclusion of physiological instrumentation into clinical trials.

**Cognitive Impairments**

It is now well accepted that pre-HD participants, in comparison to controls, show poorer performance in measures of attention, processing speed, psychomotor functions, episodic learning and memory, emotion processing, sensory perceptual functions and executive function. One report with a very large sample size of pre-HD participants suggests that cognitive decline can be detected up to 15 years prior to traditional motor diagnosis. Since nearly 150 empirical reports of cognitive function in pre-HD have been published in the past 15 years, the papers are too numerous for a comprehensive review.

Although reports cite comprehensive cognitive batteries being administered to detect early cognitive decline in pre-HD, the field is well poised to move toward greater specificity in terms of the cognitive domains that are sensitive in pre-HD prior to motor disturbances. We report specific data of over 1000 participants from the PREDICT-HD study. Findings are based on three stratified groups: a 'far from clinical diagnosis' group, estimated to be more than 15 years from diagnosis; a 'middle' group, estimated to be between 9 and 15 years from diagnosis; and a 'near diagnosis' group, estimated to be less than 9 years from diagnosis. We calculated effect sizes for 22 individual cognitive measures in comparison to demographically matched research participants who were at risk but were found to have normal CAG repeat lengths after undergoing predictive testing. We then chose the three most sensitive tasks in each conceptual cognitive domain and averaged their effect sizes. The light blue bars in Figure 5 depict the effect sizes based upon pre-HD participants near clinical diagnosis and demographically matched comparison participants.
Next, we examined the longitudinal data from PREDICT-HD. Although most of the cognitive tasks are only repeated every 2 years, some are repeated annually. Again, performance changes in pre-HD near diagnosis were compared with changes in the normal comparison group and effect sizes for longitudinal data are shown in the darker blue bars from Figure 5. Figure 6 shows the association between estimated years to clinical diagnosis (depicted along the x-axis) and several measures. For example, speeded finger tapping, timed-tap generation and word list learning all show deterioration in performance at least 15 years before the expected motor diagnosis. As shown in Figure 6, nearly all markers studied appear to follow a similar pattern of decline. Such an acceleration of decline in cognitive and motor measures has been replicated in a separate sample.\textsuperscript{62} Rupp and colleagues suggest that only some cognitive measures show acceleration of decline whereas others show a constant rate of decline throughout the prodromal period.\textsuperscript{86} Further longitudinal study is critical to the determination of the best cognitive measures for clinical trials in pre-HD.

Figure 5. Cognitive domain effect sizes for pre-Huntington's disease near estimated clinical diagnosis.

Figure 6. Relationship between estimated years to diagnosis in participants with the prodrome for Huntington's disease and various other measures. (A) Motor exam score. (B) Striatal volume. (C) Speeded finger tapping. (D)
Self-timed finger tapping, (E) Word list learning. (F) Odor identification. Solid line plots the mean; broken lines are 95% confidence limits. All relationships are adjusted for gender, age and education.

SD: Standard deviation.

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Using conventional criteria for mild cognitive impairment (MCI), it has been suggested that at least 38% of pre-HD research participants demonstrate impairment on demographically standardized assessment. Although the utility of MCI has been demonstrated for Alzheimer's disease, the efficacy of the construct for other forms of neurodegenerative diseases is unknown. However, recent efforts have begun to determine whether individuals with MCI can benefit from clinical care by healthcare professionals. It is not known whether MCI in individuals with eventual HD or other neurodegenerative disorders will show increased probability of more rapid diagnosis of brain disease than their counterparts. Prospective longitudinal study will be critical to determine whether MCI might be a useful concept in the early detection of HD as it has proved in Alzheimer's disease.

These findings reflect the wealth of published studies now demonstrating that cognitive tests are an early and sensitive measure of disease in pre-HD. In addition, findings suggest that there are several cognitive tests that may be useful for the early detection of disease, as well as cognitive tests that may be markers of decline over time. Further research is needed to delineate which specific cognitive domains and which distinct tests will be most useful in selecting participants and providing end points for clinical trials in pre-HD.

Although there is no question that cognitive performance declines during pre-HD, much remains to be researched prior to making a recommended cognitive battery for pre-HD clinical trials. Much can be learned from our colleagues who have developed collaborative batteries for other brain disorders. For example, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery was developed with government, industry and academia collaboration over a period of 4 years and included well-controlled studies of validation. Future research for clinical trials in pre-HD and HD patients requires that several cognitive studies be conducted and shared among the HD research community. First, cognitive candidates need to undergo rigorous psychometric evaluation to document the reliability, validity and repeatability of tasks considered. For example, it is possible that a task is chosen because it shows a very large effect size, although upon more careful consideration the task also shows very large error variance and poor test-retest reliability. Second, cognitive candidates are likely to vary in efficacy dependent upon disease stage. For instance, a task could be chosen owing to large change scores over time that disappear when the same task is administered to a pre-HD participant at an earlier epoch of disease or a diagnosed HD patient. Third, cognitive measures vary greatly in terms of feasibility for clinical trials. The size, portability, cost and stability of computer platforms, the need for peripheral hardware and software, the dependence upon technical stability and lack of variation (not possible in this age of computer advances), and the availability of normative standards (HD has greater normative variability than any other neurodegenerative disorder) all impact on the choice of cognitive tests. In addition, frustration tolerance, motivational factors and time constraints will impact the tasks chosen. Finally, in an era where nearly any cognitive measure can show impairment in a well-characterized pre-HD sample, it is critical that we minimize redundant publication of 'just one more test that shows impairment'. We do not need even one more task unless we work closely together to build upon what is known. There are at least two questions that should be addressed in new publications: first, does the new cognitive measure being studied improve upon current available measures? The measure should be compared with regard to reliability, cost and effect size. That is, a new measure that has greater consistency, less cost and larger effect sizes for pre-HD change over time might be a better outcome measure than a self-paced timed tapping task. Second, does the new cognitive measure add nonredundant information? If a new measure was not highly associated with self-paced timed tapping and represented an additional component of the disease process it may prove worth pursuing. Further research in the cognitive phenotype of pre-HD is needed in order to design clinical trials.

Psychiatric Aspects

Despite variations in prevalence rates for psychiatric disorders in HD, there is general agreement that neuropsychiatric symptoms constitute a distressing aspect of HD and often constitute reason for hospitalization. In addition, psychiatric symptoms in diagnosed HD have been reported to have a more robust association with functional outcomes than motor and cognitive impairments.

Although reports have suggested that psychiatric symptoms occur as many as 20 years prior to motor diagnosis, research in pre-HD has been limited. The few studies in pre-HD that exist demonstrate that irritability, obsessive checking and pathological impulses, disinhibition, apathy, depression and emotional recognition are all significantly impaired in pre-HD compared with controls. However, findings have not been unequivocal as some studies found no difference between gene-positive and gene-negative at-risk participants. The lack of consistency in findings could be a result of methodological limitations, such as small sample sizes, the use of assessment instruments that lack the sensitivity to detect subtle psychiatric changes (categorical vs dimensional measures), measuring psychological functioning in close temporal proximity to
genetic testing, unavailable or inadequate information regarding estimated time to clinical diagnosis of HD, and lacking collateral information about the participants’ psychological functioning. In a study with the largest pre-HD sample size to date (n = 681), nearly all psychiatric symptoms (e.g., depression, anxiety and obsessive-compulsiveness) were significantly greater in pre-HD participants than in normal comparison samples, and psychiatric comorbidity increased with proximity to estimated diagnosis. More recent is a report of 908 pre-HD participants, who completed the Frontal Systems Behavioral Scale. Findings demonstrated that the pre-HD group had higher scores on all three subscale measures (apathy, disinhibition and executive function) than the nonexpanded comparison group, and ratings remained significantly higher whether they were assessed via self-report or by companions. Interestingly, ratings between the pre-HD participant and a companion showed poor agreement and the discrepancy between ratings was associated with time to estimated clinical diagnosis (Figure 7). The authors have interpreted the discrepancy in behavior ratings as a possible assessment of impaired insight. Although research in clinically diagnosed HD has shown impaired awareness of cognitive, emotional and functional abilities, no known study has documented these insight problems in pre-HD. As pre-HD participants approach clinical diagnosis, impairments in insight could interfere with accurate reporting of psychiatric symptoms, and, therefore, companion reports and other objective measures might be better indicators of psychiatric distress in pre-HD.

Figure 7. Difference score between pre-Huntington’s disease participants and companions on ratings of so-called ‘frontal lobe behaviors’. Solid line represents mean and dotted line represents 95% confidence interval. Highly significant association between agreement of manifest frontal behaviors and proximity to manifest motor diagnosis. Adjusted for age (40.65 years), gender (male or female) and education (14 years).

In one of the few longitudinal studies of psychiatric symptoms in pre-HD, Langbehn and colleagues demonstrated that psychiatric symptoms were predictive of prospective clinical diagnosis in a cohort of at-risk participants who were not gene tested.

Several empirical reports have recently emerged supporting this notion that psychiatric symptoms and even psychiatric disorders precede the onset of motor and cognitive impairments in HD. However, as suggested by Rosenblatt, improved quantitative research is needed in order to refine the psychiatric syndrome of HD. For instance, recent results suggest that obsessive-compulsive symptoms in pre-HD individuals emphasize worrying and checking and rarely reach the levels of severity.
associated with diagnoses of obsessive-compulsive disorders until later in HD following clinical diagnosis. Similarly, an analysis of the depression phenotype in pre-HD suggests that cognitive difficulties (i.e., poor concentration), suicidal thoughts and low energy characterize this syndrome. Although the range of scores on traditional depression assessment observed in pre-HD was often as broad as that observed in major depressive disorder, the profile of these scores was poorly related to overall severity of depressive symptoms (suggesting poor discriminative properties) and appeared distinct from that observed in major depressive disorder.

Much work remains to be carried out in order to characterize the psychiatric phenotype of pre-HD. Biological psychiatry needs to be embraced in order to help understand how mood and anxiety manifest in pre-HD. Reliance on prototypical mental disorders has proven limited to characterize the presentation of psychiatric disturbance in pre-HD as well as manifest HD. There are at least three research areas requiring clarification. First, imaging and physiology measures would be helpful to better document the pathophysiology of psychiatric disturbance in pre-HD. Efforts using functional imaging such as those used by Kloppel et al. and Paradiso et al., have offered insight into brain mechanisms of psychiatric symptoms in HD. Second, self-report scales are probably limited by impaired insight, at least in a sizable proportion of pre-HD. Further study is needed to document insight and awareness in both HD and pre-HD and how clinical rating scales might be developed to allow valid and reliable assessments of psychiatric symptoms without sole reliance on self-report instrumentation. Third, items used from research on other neuropsychiatric disorders may require validation in pre-HD cohorts. It has been suggested that item performance can vary significantly, depending upon the cohort sampled. Preliminary findings using Item Response Theory (IRT) demonstrate that performances of pre-HD participants are not consistent with those obtained in other psychiatric disorders and will require editing and redeployment.

Clinical End Points for Clinical Trials

Although often overlooked, the identification of a clinical end point is among the most important components of clinical research. According to the FDA, clinical end points are the most credible characteristics used to interpret the results of randomized clinical trials and reflect how a patient feels, functions or survives. A major challenge for neurodegenerative disorders has been the identification of clinical outcome measures that accurately track disease. Over the past few years, research groups have critically reconsidered clinical outcome measures for multiple sclerosis, Alzheimer’s disease, amyotrophic lateral sclerosis and Parkinson's disease. Primary outcome measures used in clinical trials of patients with symptomatic HD typically involve a clinical symptom or sign (usually chorea) and a measure of everyday function. One of the most frequently used measures of function in HD is the Total Functional Capacity (TFC) scale. The TFC scale measure is a 5-item clinician rating scale typically completed after a brief interview. The TFC is a broad measure of functional capacity that globally assesses occupation, finances, domestic chores, activities of daily living and level of care, with scores on each item ranging from 0 to either 2 or 3 (e.g., occupation: 0 = unable; 1 = marginal work only; 2 = reduced capacity for usual job; 3 = normal). TFC total scores range from 0 to 13, with greater scores indicating higher functioning. A total of 89% of 786 pre-HD participants from the PREDICT-HD study were rated as having the maximum possible score on the TFC scale, whereas less than 8% of the participants lost one point, 2% lost two points, and 1% lost only three points on the TFC. In other words, over 99% of the pre-HD sample scored over 10 out of 13 on the TFC scale. Based on these findings, it is likely that outcome measures for an earlier disease epoch may need to be revised to include items of higher functional capacity. For instance, the item typically lost first for participants who later received a clinical diagnosis of HD was the item asking about accustomed employment. It is possible that work functioning measures may provide a better outcome measure for early clinical trials in HD. In addition, more sensitive measures of interpersonal relations may provide appropriate clinical outcomes for early HD. Duff and colleagues found that personality factors, such as apathy, executive control, inhibition and social cognition, were significantly impaired in pre-HD. To our knowledge, few studies have examined interpersonal relations as early outcome measures for degenerative diseases.

The need for better clinical outcome measures has reached prominence and widespread importance. In 2004, a group of scientists from seven institutions worked in partnership with the NIH to form a network funded under the NIH Roadmap for Medical Research Initiative to re-engineer the clinical research enterprise. This initiative was termed the Patient-Reported Outcomes Measurement Information System (PROMIS) and aims to revolutionize the way patient-reported outcome tools are selected and employed in clinical research and practice evaluation. Among the primary objectives of this initiative is to establish a national resource for accurate and efficient measurement of health outcomes for clinical practice. PROMIS aims to develop ways to measure patient-reported symptoms (such as pain and fatigue), functional capacity, and aspects of health-related quality of life across a wide variety of chronic diseases and conditions.

Clinical Trial Considerations in pre-HD

Clinical Diagnosis as End Point, Adjusting for Baseline Risk Factors
Given CAG length and a person's current age, probabilities of clinical diagnosis within an expected time are available\cite{12} and occur throughout the literature in pre-HD. Considering that prospectively diagnosed pre-HD participants are available (81 clinically diagnosed from 610 pre-HD participants evaluated for up to 5 years in PREDICT-HD) it was tested whether biological and/or refined clinical measures would improve the predictability of CAG-age-based prognostic models. Using backward stepwise selection procedures, a selection of refined clinical variables were added to CAG-age-based prognosis and neurological examination score predictions of clinical diagnosis. Initially, 24 measures were screened and 14 competed for inclusion in the final model. Results are listed in Table 1. The log-logistic model naturally yields results in terms of odds ratios of diagnosis. These ratios are similar to hazard ratios (more familiar to many readers) in a way analogous to odds ratios versus relative risk in studies with a single follow-up. As expected, results from the CAG-age formula significantly predict the clinical diagnosis of HD in our 81 converters. Ratings from the motor exam and four of the cognitive tests in PREDICT also significantly and independently add to the prediction of HD clinical diagnosis. Although the available sample size from MRIs was smaller, striatal volume (putamen plus caudate) was the strongest MRI predictor, and addition of this variable substantially diminished the independent significance of CAG-age-based prognosis, the Stroop and Tower 3 tests and speeded (but not self-paced) tapping. Still controlling for motor exam and self-paced tapping, striatum was a significant predictor (p = 0.006) with increased odds ratio of clinical diagnosis estimated at 1.55 per cm$^3$ (2.54 per standard deviation of striatal volume). The total predictive accuracy of this model was nearly identical to the model in Table 1. Provisionally, this suggests that similar prognostic accuracy may be obtainable from volumetric MRI measurement or a combination of genetic information and more detailed clinical examination. However, a firm conclusion should await completion of further data collection and increased sample sizes.

Table 1. Multivariate predictive model of diagnosis.

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Odds ratios are per SD of each measure among gene-expanded Neurobiological Predictors of Huntington's Disease (PREDICT-HD) subjects. Control for age and gender had no substantial effect on the above estimates.

HD: Huntington's disease; SD: Standard deviation; UHDRS: Unified Huntington's Disease Rating Scale.
The reduction in variance for cumulative diagnostic probabilities over various lengths of time can be calculated by comparing mean participant-specific (Bernoulli) variances within these nested prognostic models. The variance reductions shown in Table 2 are of substantial practical importance, as they are first-order approximations of the proportional reduction in sample size achievable in a Phase III clinical trial on a similar pre-HD cohort if the efficacy analysis adjusts for these baseline risk factors. We have confirmed this via computer modeling of 2- and 3-year trials incorporating hypothetical treatments with relative diagnosis risks of 0.6-0.8; relative efficacy assumed independent of prognostic markers. Similar prognostic estimations can be calculated using the disease burden formula suggested by Penney and colleagues, as used in the TRACK study.

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### Table 2. Proportion 'variance explained' in diagnostic probability by prognostic models.

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Statistics are adjusted $r^2$; n = 522.

**Clinical Diagnosis as End Point Using Enriched Samples**

Even more dramatic sample size benefits can be demonstrated if participants are limited to only those above median risk in the full prognostic model (Table 1). Allowing for model-construction bias, we estimate that approximately 95% of all participants diagnosed within 3 years would have higher than median baseline risk and be included in such a study. Computer modeling suggests that sample size is reducible by 50-60% by the use of such screening. If the baseline estimates are further used for statistical adjustment among those participating (similar to Table 2), sample size reductions of 60-70% appear feasible. The above clinical trial scenarios assume that prevention of clinical diagnosis is the efficacy measure and that intervention at this point in HD development can have an impact. Under these narrow assumptions, our results underscore the fact that we can identify those at such low risk for imminent diagnosis and that their inclusion in a trial can contribute very little. Balanced against risk, their participation may not only be uneconomical but also unethical.

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Put another way, findings suggest that performance on a simple task, such as tapping, can significantly improve the prediction of a participant receiving a clinical diagnosis of HD within 5 years. Moreover, these findings demonstrate that our various markers are not redundant. For instance, the tapping task continues to improve prediction even when CAG repeat length, MRI putamen volumes and the neurologist's motor rating are already considered. In summary, this preliminary analysis of incident clinical diagnosis of HD suggests several robust markers that can double the predictive power gained from CAG repeat length alone. Sample sizes needed for clinical trials can be reduced by up to 70% with various combinations of the PREDICT-HD baseline assessment.

Biological & Refined Clinical Markers as Outcomes

Since no end points currently exist for a preventive clinical trial in HD, it is encouraging that some of our measures may demonstrate significant longitudinal change over a relatively brief interval. Preventive trials reliant upon eventual clinical diagnosis are costly and time consuming, since larger numbers of participants are needed to enable a comparison of conversions between the treatment and placebo groups. Data from the PREDICT-HD cognitive battery and MRI have demonstrated that several measures of each show change easily detected within 2 years.\[36,79\] For instance, using a measure of total striatum volume repeated over 2 years, findings show that participants who are nearer to estimated clinical diagnosis have an effect size of -0.88 when compared with at-risk participants without the CAG expansion. This large effect sizes translates into the sample size needed to use MRI striatal volume as an outcome measure in a 2-year clinical trial. To detect a 50% therapeutic effect of a compound, 108 participants per treatment arm would be needed for a 2-year clinical trial, assuming a two-sided \( \alpha \)-level of 0.05 and 90% power. The 1-year longitudinal change indices will be available soon from the multinational TRACK study.\[28\]

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Outstanding Needs Prior to Preventive Trials in pre-HD

There are several issues that require resolution prior to the launch of a clinical trial for pre-HD. First, increased sample sizes obtained from PREDICT-HD for prospective diagnoses will be essential to document the association of predictive variables with actual prospective diagnosis. This will test face, concurrent and predictive validity for the emergence of refined clinical and new biomarkers. Second, the data acquired from the TRACK study for 1-year change rates is important to help determine whether change can be detected in 1 versus 2 years. It is always a challenge to design a trial long enough to allow robust change to be

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documented and short enough to expedite clinical trial findings. Third, although perhaps most importantly, partnerships between
clinical researchers and HD families are improving too slowly for the expeditious implementation of clinical trials. Current HD clinical
trials are slow to enroll, causing costs to grow at an alarming pace. As treatments are readied for study in humans, it is vital for the
participant pool to rapidly volunteer and enroll. Despite efforts by lay and professional organizations, little improvement has occurred
in this rate-limiting obstacle for clinical trials.

**When Does HD Begin?**

If one were to ask the question, 'when does the disease begin?', the correct answer today would be that we do not know. We have
not yet examined people with a CAG-expansion early enough in their lives to find a point when they appear to have no indication
of HD. To date, we have found clinical and biological indicators of disease even in groups who are estimated to be more than 15 years
from estimated clinical diagnosis.[10,23,41,50,79,123,124]

In light of the extensive findings demonstrating earlier detection of this brain disease years before its traditional diagnosis and the
availability of an unequivocal genetic marker in the form of an expanded CAG tract, we must ask ourselves 'why do we not diagnose
HD at an earlier time?' The formal diagnosis of HD is a controversial issue with important political, ethical, legal, social, medical and
research implications. The identification of pre-HD individuals with varying degrees of risk to receive a clinical diagnosis of HD is
appealing from a research perspective, because it could lead to more efficient clinical trials by using enriched samples (i.e., persons
with a higher likelihood of clinical diagnosis during a brief time interval). In addition, it is clear that an increased uptake of predictive
testing coupled with an augmentation in the propensity of individuals to volunteer for research may have the potential to expedite
advances in pre-HD. At present, these limitations may explain why the study of pre-HD requires 33 sites in seven countries. Without
considerable changes in the research and clinical arena for HD, clinical trials will require such excessive cost that our capacity to find
treatments that make a difference for persons with HD will be diminished.

From a clinical standpoint, the early identification of disease could also have advantages, such as advanced planning for medical
and legal decision making, initiating treatment plans and making lifestyle choices (e.g., childcare, work and living arrangements). However, earlier diagnosis must also be considered along with its potential risks, which might include increased stress, changes in social relationships and discrimination (e.g., loss of insurance coverage[125,126]). From a political perspective, efforts to alter the diagnostic criteria for HD will necessitate the addition of cognitive and psychiatric components, as well as the possibility of imaging criteria. For a disease that has benefited from monospecialty care for over a century, inclusion of additional criteria may present a challenge to healthcare professionals.

Earlier identification of disease is universally considered as useful when a treatment exists to slow or stop its progression. The
argument is raised that until a prevention or treatment is found it is difficult to justify the importance of earlier detection. However, with
regard to HD we need to ask the question 'treatment for what?' There may well be treatments for the HD symptoms of depression, irritability and cognitive decline, among others, that would benefit HD families. Short of a comprehensive treatment, HD families might benefit from acknowledging the way they feel about what is happening to them as the slowly progressive, insidious changes occur. At present, nobody in the prodrome of HD knows to ask about these symptoms or their treatment. Furthermore, possible treating physicians are not yet prepared to offer treatments for HD unless motor signs are evident that make them 99% confident of HD.

Historically, diagnosis in HD appears to have become code language for 'when should I tell the patient?' This was probably a
combination of personal sensitivity combined with the pre-gene demand to be certain about diagnosis so that genetic studies could
determine the locus. Unfortunately, hesitancy to diagnose HD remains. Truth telling in medicine has not always been seen as
virtuous. The Hippocratic Oath instructed physicians "what I may see or hear in the course of the treatment or even outside of the
treatment in regard to the life of men ... I will keep to myself". As late as the 1960s in the USA, over 90% of physicians said they
would conceal the diagnosis of cancer from patients.[127] In the 1970s, truth-telling became a requirement for informed consent[128]
but patient advocacy groups still had to lobby for greater patient awareness and control over medical decision making. Breaking bad
news emerged in the ethics literature as a requirement of professionalism and justice only recently.[129] It has been found that
physician attitudes and communication styles can result in behaviors designed to dull the full impact of the news and avoid full
statements of a diagnosis.[130,131] Although physicians continue to find it stressful to give a bad diagnosis, it has been reported that
patients typically can address the news without increased anxiety and that avoidance of diagnosis can have adverse outcomes.[132]

Without adequate information regarding their condition, patients may have an impaired ability to formulate their own goals. According
to standard theories of justice, all individuals have the right to make a rational life plan. Such a plan requires knowing one's aims and
facing up to all possible information and circumstances in order to form the best course of action to achieve one's personal
goals. The goal of enabling patients to become full decision-making partners with the physician can only be met when the patient has the information necessary to understand the circumstances from which they must formulate a rational life plan. The main problem in withholding information in the case of a debilitating illness "is that the reluctance to make a candid disclosure of the diagnosis ... may violate basic moral and legal rights and may deprive patients and caregivers of some of the benefits of early disclosure of diagnosis". For patients with an early diagnosis of HD, the withholding of information may mean the loss of an opportunity to seek early treatment or fulfill lifelong goals on a shortened timeline. To ensure the ability of our patients to make a rational life plan the earliest diagnosis may provide the best opportunity for the pursuit of these important individual aims.

Conclusion

Considerable data are now available regarding early indicators of HD that are detectable years (if not decades) before traditional clinical diagnosis. Usage of any one of the multiple measures reported here results in earlier detection of the pathophysiology of HD. It is important to understand what these findings may mean in the context of clinical care and research. First, the time course for HD has at least doubled. Previous reports had documented that death occurs approximately 15 years following a clinical diagnosis of HD, and current findings suggest that changes in clinical signs are evident 15 years prior to clinical diagnosis. Increased awareness of an over 30-year duration of disease is consistent with patient reports and may assist healthcare practitioners in providing better education and clinical care for HD families.

Second, these efforts to detect earlier disease have resulted in a more comprehensive characterization of HD. What was once a traditional movement disorder is now better described with three key features of basal ganglia functions: movement, cognitive and psychiatric disturbances. Although this is not news to the movement disorder specialist who has been working with these patients for decades, it is critical to expand training programs for primary care to better encompass all three components of HD as well as other movement disorders. Similarly, clinical trial efforts are in desperate need of expansion from a narrow emphasis on treatment for motor symptoms to a broader search for treatments that can provide relief for psychiatric and cognitive symptoms.

Finally, and perhaps most urgently, it is evident that the pathophysiology of HD starts long before the point at which the criteria for traditional diagnosis are satisfied. Moreover, the detectable signs and symptoms of that pathophysiology, especially when coupled with a family history and the ability to genetically confirm (i.e., avoid false positives), provide a clear medical basis for earlier diagnosis. The question is, 'why not?'

Future Perspective

Further examination of the issues raised in this article is warranted, and delay of such discussions is likely to have a direct impact on healthcare for HD families. General recommendations that may facilitate clinical and research progress in HD are listed as follows:

- Integration of the 30-year span of HD into training guidelines for HD healthcare professionals and families to allow for long-term life and treatment planning as well as an expanded research window;
- Design of a multidisciplinary training conference to develop and disseminate the HD information attained over the past decade into education and training programs for all integral specialties, including genetics, genetic counseling, nursing, psychology, psychiatry, neurology, occupational and physical therapy, neuropsychology, speech pathology, radiology and primary care;
- Encouragement for the implementation of a consensus conference to discuss which components of HD might be best used in clinical and research diagnostic criteria for HD. Universal diagnostic criteria that involves all stakeholders across disciplines and countries and has input from the lay organizations and HD families is needed;
- Development of more formal involvement of the medical community in policy planning and legal developments, such as Genetic Information Non-Discrimination Act (GINA) to protect the HD family from any consequences as they navigate living with a long-term chronic disease.

Sidebar

Executive Summary

Introduction

- Huntington's disease (HD), an autosomal-dominant progressive neurological disease with an identified gene mutation, has demonstrated insidious changes in brain morphology, motor control, cognitive skill and psychiatric symptoms over a period of 30 years.
PREDICT-HD study

- The Neurobiological Predictors of Huntington's Disease (PREDICT) study is an NIH- and Cure HD Initiative-funded multisite, longitudinal, observational study in its 9th year that is aimed at identifying biological and refined clinical markers of early HD in humans who have a gene mutation for future disease, but are currently healthy.
- Numerous markers have been identified, but require validation before they can be used as outcomes and clinical end points for use in preventive clinical trials.

Neuroimaging

- Findings from structural, as well as functional, imaging suggest that disease is present decades prior to traditional clinical diagnosis and several imaging indices appear to be candidates for markers in clinical trials.
- New technologies are challenging traditional approaches to image analysis and interpretation.
- Efforts to minimize variability from different scanners and across sites will be critical for all multisite clinical trials using imaging as an end point.

Motor signs

- Subtle motor signs are present long before a clinical diagnosis of HD is given.
- Quantitative measures of motor function are being considered as measures for clinical trials and will require extensive validation.

Cognition

- Numerous individual tasks show decline, and even impairment, decades before clinical diagnosis.
- Additional research is crucial to determine the most robust, but efficient, cognitive assessment of early HD for use in clinical trials.
- Cognitive domains of speed and dysexecutive functions appear sensitive.

Psychiatric

- Nearly all psychiatric symptoms and signs examined are elevated in pre-HD, yet syndromes do not mirror those observed in prototypical psychiatric disorders.
- Data are not yet available to determine when psychiatric symptoms begin, since they are already present in research conducted on pre-HD participants who are far from estimated clinical diagnosis.
- Measures of psychiatric ratings are difficult to ascertain, possibly owing to diminished insight, even in pre-HD.

Conclusion

- Considerable data are now available regarding early indicators of HD that are detectable years (if not decades) before traditional diagnosis.
- Diagnostic criteria for HD should be considered for revision to include all clinical characteristics (motor, cognitive and psychiatric), as well as biological characteristics (imaging).
- Earlier diagnosis is likely to advance life planning for individuals as well as research advancements for treatment.

References

   • Hallmark publication of the relationship between the length of the CAG repeat in the HD gene and the age of clinical diagnosis.
   • First publication of the 32-site PREDICT-HD multinational collaborative study of pre-HD.
   • First publication to show that HD was detectable 10-15 years before a traditional clinical diagnosis of HD, based upon manifest motor signs, was given. From this point forward, many publications refer to evidence of HD 'decades' before diagnosis.
   • Reliability study of the most widely used clinical rating scale for HD, the Unified HD Rating Scale, constructed by the multinational Huntington Study Group.
   • Most comprehensive development of a model to calculate estimated diagnosis based upon the now well-known association of CAG repeat length and age of diagnosis.
   • Provides a comprehensive review and comparison of several different formulas used to estimate the probability of clinical diagnosis in pre-HD in the literature. Findings can help interpret both past and future studies in pre-HD.
   • Elegant study demonstrating the associations between imaging variables acquired from FreeSurfer and variables of clinical phenotype in HD. As a more recent publication, a good review of Rosas' work suggesting the added importance of the cortical structures in HD.
   • Most recent publication from Aylward, whose pioneering efforts documented the importance of MRI for the assessment of striatal atrophy in HD. This publication shows the cross-sectional and longitudinal change rates in a small sample of pre-HD patients.
   • Publication of psychiatric symptoms in pre-HD using the largest sample size ever reported.
• Important study (albeit in a small sample) because it demonstrates that even a gross measure of brain imaging may be a sufficient variable for progression measurement in pre- and diagnosed HD.
• First publication of the Track-HD study, a collaborative four-site study of pre-HD and early HD.
• Positron emission tomography (PET) publication in pre-HD. One of the few suggesting the potential untapped importance of PET study as an under-utilized marker for early brain disease.
• Another hallmark publication of PET in pre-HD. This research group has gathered both cross-sectional and longitudinal data and suggest that PET may be more sensitive and may show more robust changes than other markers of very early disease.
• Study of the associations among pathology from brain specimens and CAG repeat length. The findings from this study have been used to develop a measure of 'disease burden' to document the impact of repeat length on disease parameters.
• Pre-HD performances on saccadometry tools suggest that further exploration of quantitative sensitive measures of eye function may prove useful for the detection of very early disease.
• Quantitative motor measures show utility as markers in pre-HD and diagnosed HD. Rao and his colleagues use GAITrite
and suggest that more precise measures of motor function may prove useful to document subtle changes.


• First publication of early clinical markers in a longitudinal prospective study of clinical diagnosis using data obtained from the Huntington Study Group.


• Excellent study of DSM diagnoses in pre-HD. The only known study to date that uses structured interviews to document the rate of psychiatric diagnoses in this group.


   • One of the few longitudinal studies of personality changes/psychiatric variables in pre-HD. This group was one of the first to study the pre-HD cohort and had some of the best longitudinal data available to understand very early HD.


   • This study uses a large sample size and examines ratings of personality or so-called 'frontal' behaviors in pre-HD. The study demonstrates that companion ratings may be more valuable than participant ratings in a sizable proportion of pre-HD.


   • Second publication of prospective clinical markers of future diagnosis in the Huntington Study Group database. Findings demonstrated that both subtle motor signs and cognitive performance predicted future diagnosis of disease. In addition, it was demonstrated that the participants' views of their own symptoms were predictive of imminent diagnosis.


   • Good paper to illustrate the importance of patient-reported outcomes, which has recently become of primary interest to clinical researchers and clinical trialists everywhere. The FDA's mandate to emphasize patient views has led to NIH initiatives to develop new measures to address a gap in our current tools.


**Websites**

201. List of clinical trials investigating means to alleviate or reduce symptoms and slow progression in clinically diagnosed Huntington's disease. www.hdtrials.org (Accessed December 2009)


Papers of special note have been highlighted as:

• of interest

**Authors and Disclosures**

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No writing assistance was utilized in the production of this manuscript.